REMARKS

Claims 53-84 are pending in this application. Claim 84 is added. Claims 53, 60, 61, 68, 75, and 76 are amended to correct typographic errors and for further clarity. Claim 60 is amended to an independent form according to the Examiner. Claim 84 is supported by original specification. No new matter has been introduced. Reconsideration and allowance of the claims earnestly are requested.

Enablement Rejections

On pages 2-11, items 1-6, of the office action (paper no. 27), the Examiner has rejected claims 53-83 under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification "does not reasonably provide enablement for *any* [ ]" claimed elements in claims 53-83. The Examiner also states that the specification "does not teach how to make and use *any* [ ]" claimed elements in claims 53-83, specifically, how to make and use *any* membrane localization reagent comprising *any* lipophilic binding element, hydrophilic peptide and linker region.

Applicants respectfully disagree with the Examiner and traverse the rejections. First, applicants note that an enablement rejection only can be supported when the experimentation needed to practice the claimed invention is considered 'undue' by the field. Accordingly, in making a rejection the Examiner must distinguish between routine work and undue experimentation. *See* MPEP § 2164.06 (Rev. 1, February 2003). Applicants submit that the Examiner has not done so.

In the present situation, the membrane localization reagent would be used by the skilled person in order to effect, for example, a complement activation process. As explained above, the skilled person is provided with a method of using membrane localization reagents by applicants' specification. In similar circumstances, the Federal Circuit has considered applications enabling.

An objective of this invention is to provide for membrane localization of therapeutic agents through the inventive insight that a synthetic combination of low-affinity membrane ligands combined with a linker group can provide an affinity for cell membranes while maintaining aqueous solubility. The linkage of the specified reagents to direct "cargo" (therapeutics) is independent of the nature of the cargo. Such a concept is not without precedence. For example, linkage of polyethylene glycol to proteins has concomitant benefits in terms of solubility, stability, prolonged plasma residence time, for example, and is not dependent on the nature of the protein modified. For this reason, the question of antibody specificity (at para 1, page 6 of the office action) is of no relevance, the antibody "cargo" does not mediate the primary membrane-localization process. Thus, the reagents of the invention can be applied in principle to antibodies of any specificity or indeed to any type of antibody derivative (scFv, Fab, immunoadhesin, for example).

The Examiner has cited the studies of Mikayama and Voet, which illustrate well-known facts that proteins fold in 3-dimensions and that 3-D structure can mediate highly specific biological interactions. In response, applicants indicate that Mikayama and Voet studies are not relevant to instant invention, because, the invention does not require any of the membrane-interactive components to have *any specific* 3-D structure. All that is required is that they possess the capability of interaction with components of the outer cell membrane.

Turning to the written description rejection, the USPTO has issued its final guidelines for written description (66 Fed. Reg. 1099). The written description guidelines first instruct examiners to determine what the claim as a whole covers and then review the entire specification to determine whether all subject matter that is essential to the invention is actually recited in the claims. See written description guidelines at II(A)(1), (2). Next, the examiners are instructed to determine whether the applicant was in possession of all that is claimed. See the written description guidelines at II(A)(3). According to the guidelines, possession of a claimed invention can be shown by disclosure of structural characteristics, functional characteristics that correlate with structure or combinations thereof. See the written description guidelines at

written description of the representative species of the genus can be shown by disclosure of structural characteristics, functional characteristics that correlate with structure or combinations thereof. Applicants submit that the Examiner has not satisfied these guidelines in making the rejection, which is grounds for withdrawal of the rejection.

Definiteness Rejections

On page 11, items 7-8 of the Office Action the Examiner has rejected claims 53, 60-61, 64, 68, 75 and 76 under 35 U.S.C. § 112, second paragraph. In response, applicants amend claims 60-61 and 75-76, to correct typographic errors. Withdrawal of the rejection is solicited.

Anticipation Rejections

On pages 12-14, items 9-14 of the Office Action, the Examiner has rejected the claims 53-55, 57-58, and 62-66 under 35 U.S.C. § 102(b) and alleged as being anticipated by Sigal *et al.* and Hancock *et al.* Applicants respectfully disagree with the Examiner note that in order to reject a claim under 35 USC § 102, the examiner must demonstrate that each and every claim term is contained in a single prior art reference. See Scripps Clinic & Research Foundation v. Genentech, Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 90 (Fed. Cir. 1986); see also MPEP § 2131. Claim terms are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. See MPEP §§ 707.07(g); 2111.01. Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. See In re Zletz, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111.

Not only must the claim terms, as reasonably interpreted, be present, an allegedly anticipatory reference must enable the person of ordinary skill to practice the invention as claimed. Otherwise, the invention cannot be said to have been already within the public's

Applicants provides the following explanations to assist the examiner in distinguishing the references:

(a) Sigal *et al.* describe the phenomenon of thermodynamic additivity between hydrophobic and electrostatic interactions mediated by myristoyl and basic peptide residues in the protein Src. Sigal *et al.* suggested (p. 12255 col 1) that the role of the N-terminal basic residues in Src might not be to interact with a specific receptor as had been previously suggested but might be to reduce the electrostatic potential at the surface of vesicles. Sigal *et al.* used synthetic peptides to compete for Src binding to vesicles, but they did not employ such peptides to mediate such binding in soluble proteins. There is no teaching in Sigal *et al.* of any such process of post-translational modification or any suggestion of how to achieve it in practice. Applicants point out to note that Src is an intracellular protein which does not normally exist in a soluble form outside the cell, and thus there is no teaching that directs modification of proteins in an extracellular environment. The Examiner is invited to consider paragraphs 5-7 of Dr. Smith's declaration in this regard.

Applicants further explains that Sigal *et al.* describe structural features associated with intracellular proteins that can undergo reversible interactions with the *inner* membrane leaflet. One of these features is encoded in the polypeptide chain of the protein and one (the lipophilic group) is added by enzymatic post-translational modification. Sigal *et al.* indeed establish that membrane-binding in the p21K-Ras and Src proteins is mediated by a combination of electrostatic and hydrophobic effects. Contrary to the Examiner's assertion (see page 10 of the office action), however, Sigal *et al.* do not teach how to make and apply membrane-localizing reagents in an extracellular environment.

Hence, after reading Sigal *et al.* and the many of the references cited in Sigal *et al.*, it is clear that Src is targeted to internal membranes. There is no incentive to modify an extracellular peptide with a membrane localizing motif from Src as this motif clearly targets Src only to an

Hancock *et al.* also describe the structural features associated with intracellular proteins that can undergo reversible interactions with the *inner* membrane leaflet. One of these features is encoded in the polypeptide chain of the protein and one (the lipophilic group) is added by enzymatic post-translational modification. Hancock *et al.* do indeed establish that inner membrane-binding in the p21K-Ras and Src proteins is mediated by a combination of electrostatic and hydrophobic effects. Contrary to the Examiners's assertion (see page 10 of the office action), however, Hancock *et al.* also do not teach how to make and apply membrane-localizing reagents. Hancock, in fact uses a rabbit reticulocyte lysate system for *in vitro* translation of mRNA to give precursor proteins which are then processed internally. Incidentally, Hancock also reports that methylesterification is required for efficient membrane binding, which is not required in the present invention.

Therefore, Sigal *et al.* and Hancock *et al.* do not anticipate the current invention. Withdrawal of the rejections is requested.

Obviousness Rejections

At the outset, Applicants note the Examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *see also* MPEP §§ 2142-43.

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the

Johnson & Son, Inc., 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986). Applicants submit that the rejections do not meet this test.

On pages 14-17, items 12-14 of the Office Action, the Examiner has rejected claims 53, 67, 68-70, 72-73, 77-78 and 80-81 as obvious over Sigal *et al.* in combination with Citro *et al.* On pages 17-19, items 15 of the Office Action, the Examiner has rejected claims 53, 67-74, 77-78 and 81 as obvious over Hancock *et al.* in combination with Citro *et al.* On pages 19-21, items 16 of the Office Action, the Examiner has rejected claims 68 and 82-83 as obvious over Sigal *et al.* or Hancock *et al.* each in combination with US Pat No. 5,472,939 and Citro *et al.* On pages 21-23, items 17 of the Office Action, the Examiner has rejected claims 68 and 82 as obvious over Sigal *et al.* or Hancock *et al.* each in combination with Citro *et al.* and EP 0,207,589 A1, or EP 0,155,387 A2, or US Pat No. 5,326,700. On pages 23-24, items 18 of the Office Action, the Examiner has rejected claims 53, 66, 68 and 81 as obvious over Sigal *et al.* or Hancock *et al.* each in combination with EP 0,109,653 or EP 0,152,736.

Each of these rejections depends upon Sigal and/or Hancock., which are discussed above. Simply put, Sigal and Hancock discuss natural phenomena that occur insider the cell, whereas applicants' invention is an inventive approach for localizing molecules to the outside of cells at the outer membrane. There are no teachings in the secondary references that would change the skilled person's view of Sigal and Hancock, and thus there is no combined teaching in the references that would allow the skilled person achieve applicants' invention with a reasonable expectation of success. Accordingly, the obviousness rejections should be withdrawn.

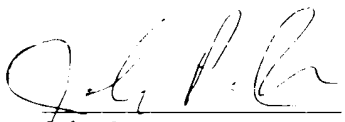
Claim Objections

On page 25, item 19 of the Office Action the Examiner has objected to claim 60 as being dependent upon a base claim, which is not yet allowed. As suggested by the Examiner,

CONCLUSION

In view of the foregoing remarks and amendments, reconsideration of the application and allowance of the claims are requested. If any issues remain which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at 202-912-2777.

Respectfully submitted,



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